rpth research & practice in thrombosis & haemostasis

LB 01.1 | Subcutaneous Prophylaxis with the Anti-TFPI Monoclonal Antibody Concizumab in Hemophilia A and Hemophilia A/B with Inhibitors: Phase 2 Trial Results

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Background: We present results from the concizumab explorer4 (NCT03196284; randomized) and explorer5 (NCT03196297; single-arm) phase 2 trials (main phase: 24 weeks).

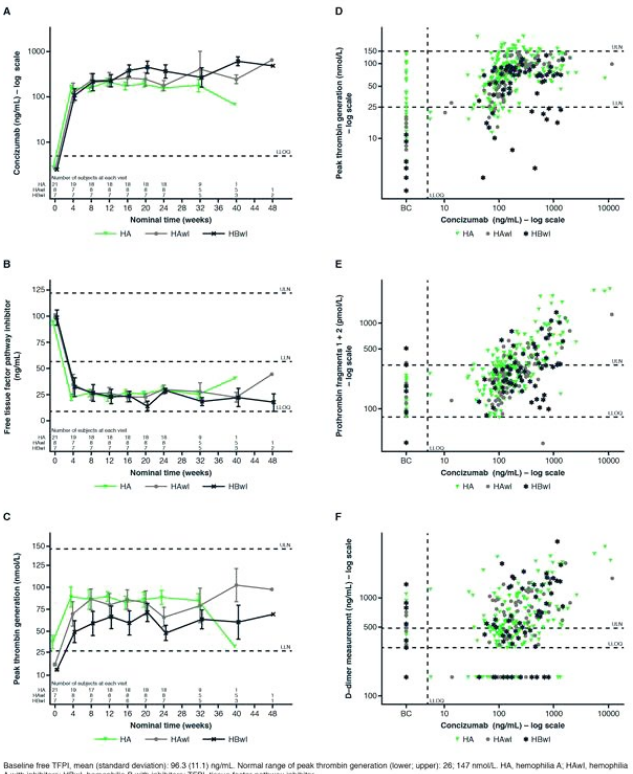
Aims: To assess the safety, efficacy and immunogenicity of once-daily, subcutaneous concizumab prophylaxis in patients with hemophilia A/B with inhibitors (HAwI/HBwI) and hemophilia A without inhibitors (HA), and to establish a dose regimen for the phase 3 trials.

Methods: Informed consent and ethics committee approval were obtained. Thirty-six HA, nine HAwI and eight HBwI patients were exposed to concizumab. Patients received 0.15 mg/kg concizumab with potential dose escalation to 0.20 and 0.25 mg/kg. The number of adverse events (AEs) was evaluated, as well as coagulation-related parameters (D-dimer and prothrombin fragment 1+2 [F1+2]). Immunogenicity was assessed by the number of anti-drug antibodies (ADAs). Concizumab and free tissue factor pathway inhibitor (TFPI) plasma levels were measured by ELISA, and peak thrombin generation (TG) potential by a standardized assay.

Results: Clinical proof-of-concept (CPoC) for once-daily subcutaneous concizumab prophylaxis was established, there were no thromboembolic events, no AE-related withdrawals, no safety concerns with breakthrough-bleed treatment, and annualized bleeding rates after 24 weeks were estimated at 3.0–7.0, with all patients choosing to continue to the extension phase in both trials. Concizumab exposure, free TFPI reduction and TG potential were similar across all hemophilia patients (Fig.1A–C), and concizumab exposure was associated with normalized TG potential (Fig.1D). With increasing concizumab concentration, elevated F1+2 were detected (Fig.1E), and there was a tendency for elevated D-dimers (Fig.1F). Three patients in each trial had ADA-positive tests, with no apparent impact on any measured parameters.

Conclusions: Phase 2 trial results confirmed CPoC, with no unexpected safety signals and have guided selection of the phase 3 dosing regimen. Further development of concizumab as a prophylactic treatment for all hemophilia patients is supported, including HBwI patients who currently have no prophylactic options.

Figure 1. Mean plots for patients with last dose level of concizumab 0.15 mg/kg (**A–C**) and for all dose levels (**D–F**) in the main phase of explorer4 (HAwI/HBwI) and explorer5 (HA without inhibitors) of (**A**) concizumab plasma concentration vs time; (**B**) free TFPI vs time; (**C**) peak thrombin generation potential vs time; (**D**) peak thrombin generation potential vs concizumab plasma concentration; (**E**) prothrombin fragments 1+2 vs concizumab plasma concentration; and (**F**) D-dimers vs concizumab plasma concentration, by hemophilia type.



Baseline free TFPI, mean (standard deviation): 96.3 (11.1) ng/mL. Normal range of peak thrombin generation (lower; upper): 26; 147 nmol/L. HA, hemophilia A; HAwI, hemophilia A with inhibitors; HBwI, hemophilia B with inhibitors; TFPI, tissue factor pathway inhibitor

FIGURE 1

LB 01.2 | First-in-human Evidence of Durable Therapeutic Efficacy and Safety of AAV Gene Therapy Over Three-years with Valoctocogene Roxaparvovec for Severe Haemophilia A (BMN 270-201 Study)

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Background: Gene therapy is increasingly viewed as a viable treatment option for hemophilia A (HA), using AAV mediated Factor VIII (FVIII) gene transfer. Interim Phase 1/2 data from valoctocogene roxaparvovec (AAV5-hFVIII-SQ) have shown promising results. Outstanding questions for all AAV gene therapies relate to clinical effectiveness and durability.

Aims: Assessment of long-term safety, efficacy, and durability of AAV5-hFVIII-SQ in a Phase 1/2 clinical study.

Methods: Adult male study participants with severe HA received a single intravenous dose of AAV5-hFVIII-SQ at 6×10^{13}vg/kg (n=7) or 4×10^{13}vg/kg (n=6).

Results: All study participants demonstrated clinically meaningful FVIII activity levels with reductions in bleeds and FVIII usage (Figure 1). Following withdrawal from prophylaxis, annualised bleeding rate (ABR) declined from pre-treatment mean by 96% at year three in 6×10^{13}vg/kg participants, and 92% at year two in 4×10^{13}vg/kg participants (Figure 2). FVIII levels reported by chromogenic assay correspond with the continued absence of target joints and target joint bleeds from years two through three. Expression levels over time are determined to decline as a function of both time post-administration and level of expression achieved, nearing a plateau of expression in year three. Accordant modelling projections conservatively estimate the persistence of bleeding control for at least eight years post-administration and longer if expression plateaus are maintained, as observed in prior AAV gene therapy studies (Figure 1). The safety profile of valoctocogene roxaparvovec remains favourable and unchanged, with no inhibitor development or ALT elevations beyond year one. Detailed durability, safety, and efficacy data will be shared at ISTH.

Conclusions: Gene transfer with valoctocogene roxaparvovec has resulted in substantial and sustained FVIII activity levels, clinically relevant reductions in self-reported bleeding episodes, and significant reductions in FVIII replacement infusions for up to three years post-dosing.

*This study was approved by a recognized medical ethics committee at each participating site. All participants provided informed consent.

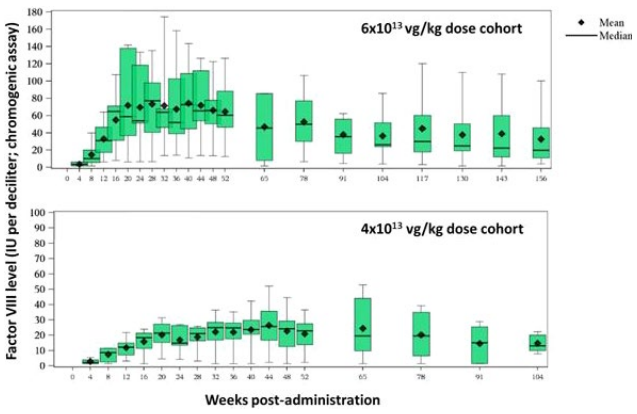

FIGURE 1 Factor VIII levels by dose cohort over time

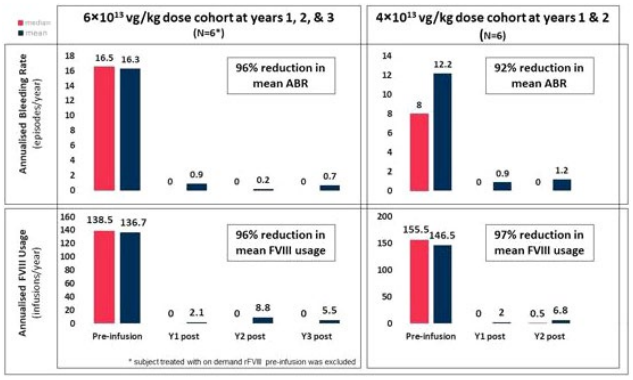

FIGURE 2 Annualised bleeding rates and FVIII usage by dose cohort over time

LB 01.3 | A Multicenter Trial of Vena Cava Filters in Severely-Injured Patients

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Background: It is not known whether early placement of an inferior-vena-cava filter reduces death or pulmonary embolism in severely-injured patients with a contraindication to anticoagulant prophylaxis.

Aims: We aimed to assess whether insertion of a retrievable vena cava filter within 72 hours of trauma admission reduces mortality or symptomatic pulmonary embolism.

Methods: In this multicenter randomized-controlled-trial, 240 severely-injured patients - with an Injury-Severity-Score (ranges between 0 and 75 with higher scores indicating more severe injury) >15 and contraindications to anticoagulants - were randomly allocated to receive a vena cava filter or no filter within the first 72 hours of admission. The primary outcome was a composite of 90-day mortality or symptomatic pulmonary embolism; secondary outcomes included symptomatic pulmonary embolism between day 8 and 90 for the subgroup of patients who survived at least 7 days and did not receive prophylactic anticoagulation within 7 days after injury. All patients received screening lower limb ultrasound at 2 weeks, and mandatory computed-tomography pulmonary-angiography when prespecified criteria were met.

Results: The median age and Injury-Severity-Score of the patients were 39 years and 27, respectively. Compared to no filter, early filter placement did not significantly reduce the primary outcome (13.9% vs 14.4%, respectively; hazard ratio 0.99, 95% CI 0.51-1.94, P=0.98). In those who did not receive anticoagulant prophylaxis within 7 days after injury, none in the filter group compared to five in the control group developed pulmonary embolism, including one fatal event (0% vs 14.7%, respectively, relative risk: 0, 95%CI 0.00-0.55). Entrapped thrombus within the filter was found in six patients (4.9%).

Conclusions: Early prophylactic placement of a vena cava filter after major trauma did not reduce the primary composite outcome of 90-day mortality or symptomatic pulmonary embolism.

(ACTRN trial number: 12614000963628)

LB 01.4 | Magnetic Resonance Direct Thrombus Imaging Can Safely Rule Out Recurrent Ipsilateral Deep Vein Thrombosis of the Leg - The Theia study

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Background: The diagnosis of recurrent ipsilateral deep vein thrombosis (DVT) of the leg is challenging because of frequent persistent intravascular abnormalities after previous DVT. Magnetic Resonance Direct Thrombus Imaging (MRDTI), a technique without intravenous contrast and with a 10-minute acquisition time, has been shown to reliably distinguish acute recurrent DVT from chronic DVT (Figure 1).

Aims: To evaluate the safety of ruling out recurrent ipsilateral DVT of the leg by normal MRDTI.

Methods: The Theia study is a multicentre, international diagnostic management study (NCT02262052) in patients with suspected acute recurrent ipsilateral DVT of the leg. Main exclusion criteria were concurrent suspected pulmonary embolism (PE) or previous ipsilateral DVT ≤6 months before presentation. The final treatment decision was based on the MRDTI result alone, which was performed within 24 hours of study inclusion. The primary endpoint was the 3-month incidence of venous thromboembolism (VTE) in patients with normal MRDTI at baseline. A VTE incidence with an upper limit of the 95% confidence interval (95%CI) below 6.6% was deemed safe. We also determined the interobserver agreement of MRDTI reading. All endpoints were adjudicated by an independent committee. The study was approved by all local IRBs. All patients provided written informed consent.

Results: Of 444 patients screened between May 2014 and March 2019, 305 (69%) were included (Figure 2). The baseline prevalence of recurrent DVT was 37%; thrombophlebitis was diagnosed in an additional 4.6%. The primary endpoint occurred in 2 of 121 (1.7% (95%CI 0.20-5.8)) patients with normal MRDTI who did not receive any form of (prophylactic) anticoagulation during follow-up; neither of these recurrences was fatal. The agreement between initial local reading and post-hoc central reading of the MRDTI images was excellent (kappa statistic 0.92).

Conclusions: Recurrent ipsilateral DVT can safely be ruled out by MRDTI alone, which can replace the often non-conclusive compression ultrasound in these patients.

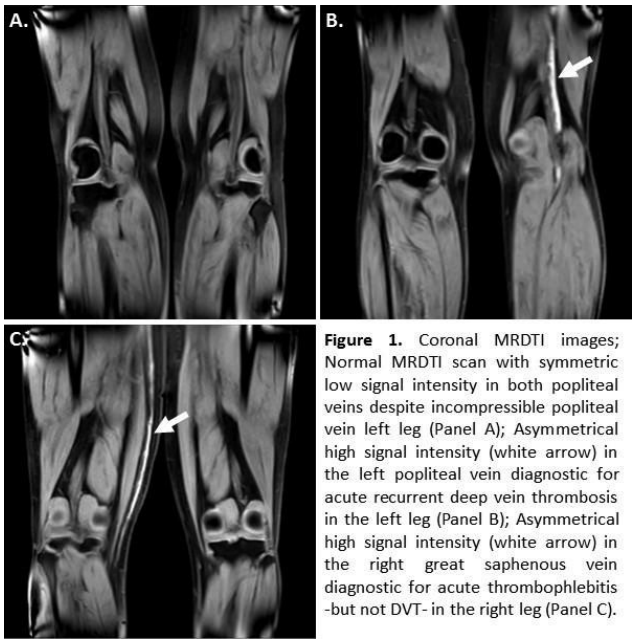


Figure 1. Coronal MRDTI images; Normal MRDTI scan with symmetric low signal intensity in both popliteal veins despite incompressible popliteal vein left leg (Panel A); Asymmetrical high signal intensity (white arrow) in the left popliteal vein diagnostic for acute recurrent deep vein thrombosis in the left leg (Panel B); Asymmetrical high signal intensity (white arrow) in the right great saphenous vein diagnostic for acute thrombophlebitis -but not DVT- in the right leg (Panel C).

FIGURE 1 Coronal MRDTI imgages

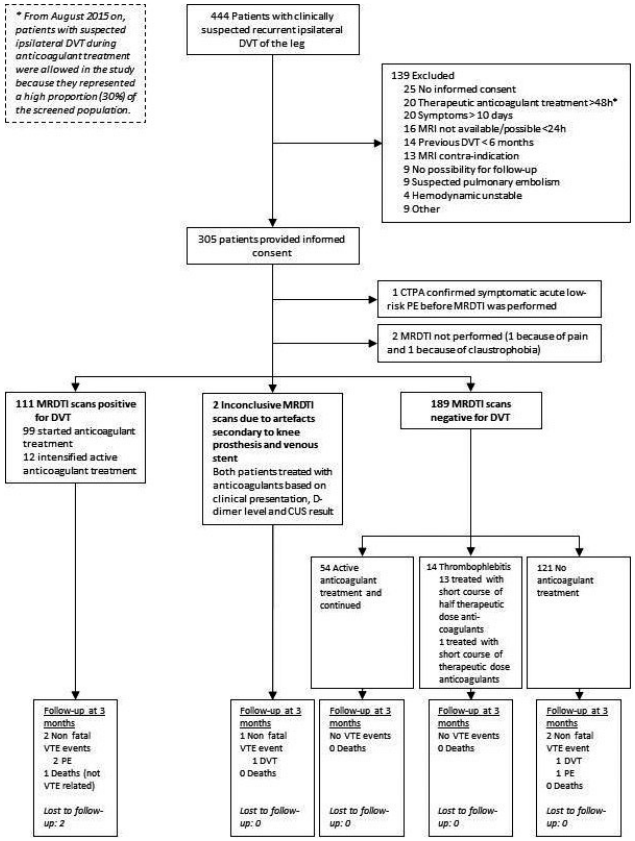
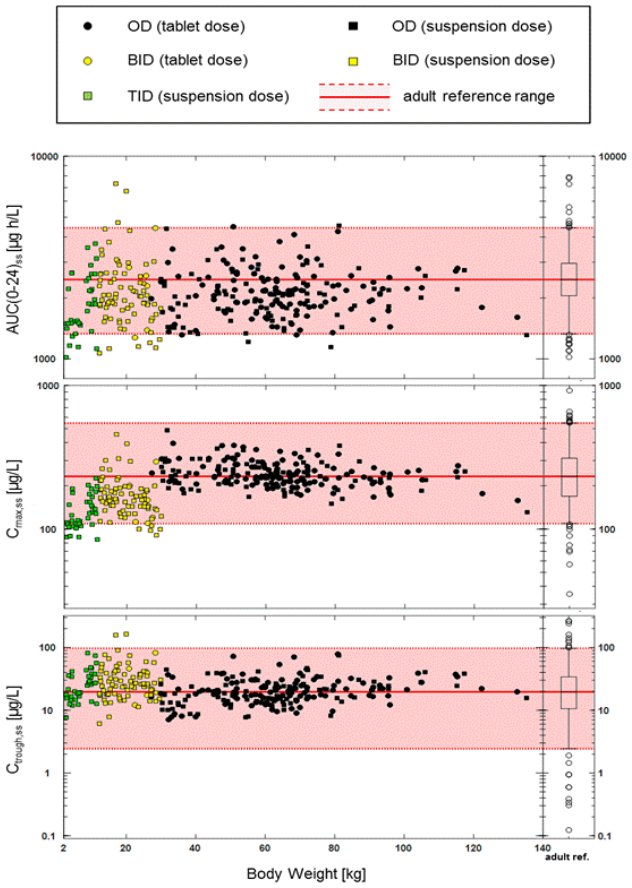


FIGURE 2 Study flowchart



Population PK results for adult VTE patients treated with rivaroxaban 20 mg once-daily are shown as box whisker plot (5, 25, 50, 75, and 95 percentiles, extremes as open circles).

FIGURE 1 Individual population PK parameters for rivaroxaban at steady state as a function of bodyweight

LB 01.5 | Rivaroxaban for the Treatment of Acute Venous Thromboembolism in Children

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Background: Treatment of venous thromboembolism (VTE) in children is currently mostly based on adult data. Bodyweight-adjusted rivaroxaban regimens had previously been established for children (birth-17 years) to match the exposure range of young adults treated with rivaroxaban 20 mg once-daily.

Aims: To compare the efficacy and safety of rivaroxaban with standard anticoagulants (comparator) for treatment of acute VTE in children.

Methods: 500 children (birth-17 years) with acute VTE (lower extremity 33.0%, cerebral veins 23.4%, lungs 16.0%, upper extremity 11.6%, jugular vein 10.4%) were randomized (2:1 ratio) to receive open-label rivaroxaban (tablets or suspension) in bodyweight-adjusted 20-mg equivalent dose regimens or comparator. The main treatment period was 3 months (1 month in children < 2 years with catheter-related VTE). Symptomatic recurrent VTE and bleeding were centrally assessed unaware of treatment assignment. End of treatment repeat imaging was obtained. Pharmacokinetic (PK) and pharmacodynamic (PD) data were collected.

Results: Recurrent VTE occurred in 4/335 (1.2%) rivaroxaban-recipients and in 5/165 (3.0%) comparator-recipients (hazard ratio 0.40, 95% confidence interval, 0.11 to 1.41). Repeat imaging showed an improved effect of rivaroxaban on thrombotic burden as compared with comparator (table). Clinically relevant bleeding occurred in 10 children (3.0%; all nonmajor) with rivaroxaban and in 3 children (1.9%; two major; 1 nonmajor) with comparator. Absolute/relative efficacy and safety estimates of rivaroxaban and comparator were similar to those obtained in adults. PK parameters for rivaroxaban confirmed plasma levels in children equal to those achieved in adult

TABLE 1 Change in thrombotic burden on repeat imaging at the end of the main treatment period as compared to the index event

Thrombotic burden on repeat imaging	Rivaroxaban (n=335)	Comparator (n=165)
Normalised	129 (38.5%)	43 (26.1%)
Improved	130 (38.8%)	75 (45.5%)
Uncertain	55 (16.4%)	28 (17.0%)
No relevant change	16 (4.8%)	13 (7.9%)
Deterioration	1 (0.3%)	1 (0.6%)
Symptomatic recurrent VTE	4 (1.2%)	5 (3.0%)

van Elteren test for comparison of ordered categories, p=0.009.

VTE trials that showed efficacy of rivaroxaban (figure). PK and PD were closely correlated. Clinical and PK/PD results were similar for rivaroxaban tablets and suspension.

Conclusions: In children with VTE, treatment with bodyweight-adjusted rivaroxaban (tablets or suspension) resulted in low recurrence risk and reduced thrombotic burden without increased bleeding compared to standard anticoagulants. Our results are comparable to those obtained in adults with VTE treated with rivaroxaban.

AUTHOR INDEX